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| 10/635,924 | 08/05/2003 | Kim Sze Tan | GJE04.FD1 | 1060 |

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| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/635,924 | TAN, KIM SZE | |
| | Examiner | Art Unit | |
| | David J. Blanchard | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/108,728.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The preliminary amendment filed 18 November 2003 has been entered in full.

2. Claims 1-16 are pending and under examination.

### *Information Disclosure Statement*

3. The information disclosure statement (IDS) submitted on 03 May 2004 has been fully considered by the examiner. A signed copy of the IDS submitted on 03 May 2004 is included with the instant Office Action.

### *Specification*

4. The disclosure is objected to because of the following informalities:

a. The specification at pg. 10, line 1, states "monoclonal ovin", which appears to be a typo. Applicant's cooperation is requested in reviewing the entire disclosure for additional minor informalities that require correction.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention i.e., "High Affinity Humanized and Chimeric Monoclonal Antibodies" or similar title that clearly describes the claimed invention.

Appropriate correction is required.

### *Claim Objections*

5. Claim 9 is objected to because of the following informalities:

Claim 9 recites "comprises variable region", which is grammatically incorrect. Consider revising with "comprises the variable regions". Similarly, line 2 of the claim should be amended to recite "the variable regions of said chimeric" for consistency and antecedent basis.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "said humanized monoclonal antibody". There is insufficient antecedent basis for this limitation in the claim. Base claim 9 from which claim 15 depends does not recite any humanized monoclonal antibody.

### *Claim Rejections - 35 USC § 112*

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized monoclonal antibody or antigen-binding fragment thereof, wherein the humanized monoclonal antibody or antigen-binding fragments thereof comprise six CDRs (hypervariable regions), three from the VH domain and three from the VL domain of a high affinity non-rodent, non-human monoclonal antibody, wherein the humanized monoclonal antibody or antigen-binding fragments retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody, does not reasonably provide enablement for a humanized monoclonal antibody or antigen-binding fragment thereof, wherein the humanized monoclonal antibody or antigen-binding fragments thereof comprises a CDR (a hypervariable region) from a high affinity non-rodent, non-human monoclonal antibody, wherein the humanized monoclonal antibody or antigen-binding fragments do not retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered or humanized antibodies where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to humanized antibodies or antigen-binding fragments thereof that only comprise a hypervariable region (a CDR) from a high affinity non-rodent, non-human monoclonal antibody and do not retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody. Thus, the claims encompass humanized monoclonal antibodies or antigen-binding fragments thereof that do not contain a full set of 6 CDRs from the variable heavy and variable light chain regions and do not retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody.

The specification discloses only humanized antibodies that contain all six CDRs from a high affinity non-rodent, non-human monoclonal antibody and the humanized antibodies bind the same antigen as the parental high affinity non-rodent, non-human monoclonal antibody (see Examples). The specification does not teach humanized antibodies or antigen-binding fragments thereof, which do not contain all 6 CDRs from the same high affinity non-rodent, non-human monoclonal antibody and do not bind antigen. There are no working examples of a humanized antibody or antigen-binding fragment thereof that only comprises a hypervariable region (CDR) from a high affinity non-rodent, non-human

monoclonal antibody and retains the antigen specificity of the high affinity non-rodent, non-human monoclonal antibody. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982). Rudikoff et al. teach that the alteration of a

single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that humanized antibodies and antigen-binding fragments thereof as defined by the claims, which contain less than the full complement of CDRs from the heavy and light chain variable regions of a high affinity non-rodent, non-human monoclonal antibody have the required antigen-binding function. There is insufficient direction or guidance provided to assist the skilled artisan in producing a humanized antibody or antigen-binding fragment thereof containing fewer than 6 CDRs or only one CDR from a high affinity non-rodent, non-human monoclonal antibody where the other five CDRs are from a different monoclonal antibody or from different monoclonal antibodies, and the humanized antibody or antigen-binding fragment thereof binds antigen. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing a humanized antibody or antigen-binding fragment thereof containing fewer than 6 CDRs or only one CDR from a high affinity non-rodent, non-human monoclonal antibody where the other five CDRs are from a different monoclonal antibody or from different monoclonal antibodies, resulting in a humanized antibody that binds antigen or retains the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the humanized antibodies as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E. and Rudikoff et al, the lack of guidance and

direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed humanized antibodies comprising only one hypervariable region or CDR from a high affinity non-rodent, non-human monoclonal antibody wherein the humanized antibodies retain the antigen specificity of the parental high affinity non-rodent, non-human monoclonal antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed humanized antibodies and absent working examples providing evidence which is reasonably predictive that the claimed humanized antibodies bind antigen, particularly the antigen of the parental high affinity non-rodent, non-human monoclonal antibody, commensurate in scope with the claimed invention.

### *Priority*

10. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 08/108,728, filed on 9/1/1993

### *Claim Rejections - 35 USC § 102*

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before

> the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-2 and 4-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Queen et al (U.S. Patent 5,530,101, priority at least to 12/19/1990).

The claims are being interpreted as drawn to a humanized monoclonal antibody or antigen-binding fragment thereof comprising the hypervariable regions (i.e., CDRs) from a high affinity, non-rodent, non-human monoclonal antibody and human framework an constant regions, wherein said high-affinity non-rodent, non-human monoclonal antibody having an antigen binding affinity of at least about $10^{11}$ l/mol and wherein the humanized monoclonal antibody has an antigen binding affinity of at least $10^{12}$ l/mol, 5 X $10^{12}$ l/mol, $10^{13}$ l/mol or $10^{14}$ l/mol and wherein the antigen-binding fragment is a F(ab')2, Fab or an Fv fragment.

Queen et al teach humanized monoclonal antibodies comprising CDRs from a rabbit monoclonal antibody (i.e., non-rodent, non-human antibody monoclonal antibody) and human framework and constant regions wherein the humanized monoclonal antibodies have antigen-binding affinities stronger than $10^{10}\,M^{-1}$ (l/mol) (see entire document, particularly col. 10, lines 55-65, col. 12, col. 16, line 60 to col. 17, line 9). Therefore, as a property is inherent to a product the rabbit monoclonal antibody, i.e., non-rodent, non-human monoclonal antibody must have had prior to humanization an antigen-binding affinity stronger than $10^{10}\,M^{-1}$. Further, Queen et al teach F(ab')2, Fab and Fv fragments (see col. 11).

Thus, Queen et al anticipate the claims.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Groves et al (Veterinary Immunology and Immunotechnology, 23:1-14, 1989, IDS reference R16, filed 4/30/04) in view of Ehrlich et al (Clinical Chemistry, 34(9):1681-1688, 1983, IDS reference R17, filed 4/30/04) and Queen et al (U.S. Patent 5,530,101, priority at least to 12/19/1990) and Steward et al (Antibody Affinity: Thermodynamic aspects and biological significance" CRC Press Inc. (1983), pp.145-153, IDS reference R19, filed 4/30/04).

Claims 1-2 and 4-7 have been described supra.

Claims 3 and 8 recite wherein the non-rodent, non-human monoclonal antibody is an ovine antibody.

Groves et al teach high affinity ovine monoclonal antibodies (prouduced from mouse x sheep heterohybridomas) for therapeutic use, the high affinities of ovine monoclonal antibodies is one advantage of non-rodent over rodent antibodies and Groves et al teach the heterohybridomas as a starting point for the production of engineered antibodies to improve effector functions including antibodies that combine components from two or more species (see entire document, particularly Table 1, bottom of pg. 9, and pg. 10). Groves et al do not specifically teach humanized ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol. These deficiencies are made up for in the teachings of Ehrlich et al and Queen et al and Steward et al.

Ehrlich et al teach that the use of a sheep anti-digoxin Fab fragment is limited to life-threatening situations due to its immunogenicity in humans (see entire document, particularly pg. 1687, 1$^{st}$ col.)

Queen et al teach humanized monoclonal antibodies comprising CDRs from a non-rodent, non-human monoclonal antibody (i.e., rabbit monoclonal antibody) and human framework and constant regions wherein the humanized monoclonal antibodies have antigen-binding affinities stronger than $10^{10}\,M^{-1}$ (l/mol), are less immunogenic in human patients and because the effector portion is human, humanized antibodies interact better with the human immune system (see entire document, particularly col. 10, lines 55-65, col. 12, col. 16, line 60 to col. 17, line 9 and col. 16, lines 9-13).

Steward et al teach that the art recognized that high antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological functions, such as neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation (i.e., effector function), ect, which are clearly mechanisms that are exploited in passive immunotherapy (see e.g., Steward et al, pg. 146, Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce high affinity humanized ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce high affinity humanized ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy in view of Groves et al and Ehrlich et al and Queen et al and Steward et al because Groves et al teach high affinity ovine

monoclonal antibodies (produced from mouse x sheep heterohybridomas) for therapy, the high affinities of ovine monoclonal antibodies is one advantage of non-rodent over rodent antibodies and Ehrlich et al teach that the use of a sheep anti-digoxin Fab fragment is limited to life-threatening situations due to its immunogenicity in humans and Queen et al teach humanized monoclonal antibodies comprising CDRs from a non-rodent, non-human monoclonal antibody (i.e., rabbit monoclonal antibody) that are less immunogenic in human patients hence, better suited for human therapy and wherein the humanized monoclonal antibodies have antigen-binding affinities stronger than $10^{10}\,M^{-1}$ (l/mol) and Steward et al teach that high antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological functions, such as neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation (i.e., effector function), ect, which are clearly mechanisms that are exploited in passive immunotherapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to reduce the immunogenicity of the high affinity ovine monoclonal antibodies of Groves et al using the humanization method of Queen et al thereby overcoming the limitations of sheep antibodies for human therapy due to their immuogenicity as taught by Ehrlich et al and because the effector portion is human, the humanized ovine monoclonal antibodies will interact better with the human immune system, an additional advantage recognized by Groves et al, who suggests using heterohybridomas (i.e., ovine monoclonal antibodies) as a starting point for the production of engineered antibodies to improve effector functions including

antibodies that combine components from two or more species. Further, one of ordinary skill in the art would have been motivated at the time the invention was made to produce high affinity humanized ovine monoclonal antibodies that are superior to lower affinity antibodies in neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation (i.e., effector functions), ect, which are clearly mechanisms that are exploited in passive immunotherapy. Thus, there would be several advantages to using high affinity humanized ovine antibodies for human therapy. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce high affinity humanized ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy in view of Groves et al and Ehrlich et al and Queen et al and Steward et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Groves et al (Veterinary Immunology and Immunotechnology, 23:1-14, 1989, IDS reference R16, filed 4/30/04) in view of Ehrlich et al (Clinical Chemistry, 34(9):1681-1688, 1983, IDS reference R17, filed 4/30/04) and Morrison S. L. (Science, 229:1202-1207, 1985, IDS reference R22 filed 4/30/04) and Steward et al (Antibody Affinity: Thermodynamic aspects and biological

significance" CRC Press Inc. (1983), pp.145-153, IDS reference R19, filed 4/30/04).

The claims are drawn to chimeric monoclonal antibodies comprising variable regions (heavy and light) from a high affinity, ovine monoclonal antibody (i.e., non-rodent, non-human monoclonal antibody) and human constant regions, wherein said high-affinity non-rodent, non-human chimeric monoclonal antibody or antigen-binding fragments thereof (F(ab')2, Fab, Fv) have an antigen binding affinity of at least about $10^{11}$ l/mol and wherein the chimeric monoclonal antibody has an antigen binding affinity of at least $10^{12}$ l/mol, 5 X $10^{12}$ l/mol, $10^{13}$ l/mol or $10^{14}$ l/mol.

Groves et al have been described supra. Groves et al do not specifically teach chimeric ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol. These deficiencies are made up for in the teachings of Ehrlich et al and Morrison and Steward et al.

Ehrlich et al have been described supra.

Morrison S. L. teach chimeric antibodies comprising non-human variable regions and human constant regions and chimeric antibodies should exhibit the effector function associated with the human constant regions and should be less antigenic in humans than are totally non-human antibodies (see entire document, particularly pp. 1205 and 1207).

Steward et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce high affinity chimeric ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce high affinity chimeric ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy in view of Groves et al and Ehrlich et al and Morrison and Steward et al because Groves et al teach high affinity ovine monoclonal antibodies (produced from mouse x sheep heterohybridomas) for therapy, and the high affinities of ovine monoclonal antibodies is one advantage of non-rodent over rodent antibodies and Ehrlich et al teach that the use of a sheep anti-digoxin Fab fragment is limited to life-threatening situations due to its immunogenicity in humans and Morrison teach chimeric antibodies comprising non-human variable regions and human constant regions and chimeric antibodies should exhibit the effector function associated with the human constant regions and should be less antigenic in humans than are totally non-human antibodies and Steward et al teach that high antibody affinity is superior to lower antibody affinity in terms of mediating a number of biological functions, such as neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation (i.e., effector function), ect, which are clearly mechanisms that are exploited in passive immunotherapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to reduce the immunogenicity of the high affinity ovine monoclonal

antibodies of Groves et al by producing chimeric ovine monoclonal antibodies as taught by Morrison and suggested by Groves et al who states that heterohybridomas will provide material for the manipulation of Ig genes and allow the engineering of antibodies to improve on effector functions and "permit the generation of chimaeric antibodies combining components from two or more species" (Groves et al at pg 10). Additionally, because the effector portion is human, the chimeric ovine monoclonal antibodies will interact better with the human immune system, an additional advantage recognized by Groves et al and Morrison. Further, one of ordinary skill in the art would have been motivated at the time the invention was made to produce high affinity chimeric ovine monoclonal antibodies that are superior to lower affinity antibodies in neutralization of toxins, virus neutralization, protection against bacterial infections, complement fixation (i.e., effector functions), ect, which are clearly mechanisms that are exploited in passive immunotherapy. Thus, there would be several advantages to using high affinity chimeric ovine antibodies for human therapy. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce high affinity chimeric ovine monoclonal antibodies having an affinity of at least $10^{11}$ l/mol for human therapy in view of Groves et al and Ehrlich et al and Morrison and Steward et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

***Conclusion***

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827